

Editorial

# Lithium in Drinking Water for Dementia and Suicide

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Bipolar disorder has been reported to be associated with increased risk of dementia [1,2] and the risk may increase with every new affective episodes [3] while lithium, which is the first-line agent for bipolar disorder, may reduce the risk of dementia because long-term lithium treatment significantly reduces tau phosphorylation and amyloid  $\beta$  production, increases synaptic plasticity and facilitates long-term potentiation and cell firing, most of which are due to GSK-3 inhibition [4]. Epidemiological studies revealed that continued lithium treatment was associated with reduction of the rate of dementia to the same level as that for general population [5] and the effects were not found in anticonvulsants, antidepressants, or antipsychotics [6], suggesting a specific effect of lithium. In a clinical setting, 35 patients who were 60 years or older without initial diagnosis of dementia and had previously received lithium treatment and/or were currently prescribed lithium had significantly better Mini-mental State Examination (MMSE) scores than 20 control patients [7]. Moreover, Alzheimer's disease was diagnosed in 3 of 66 (5%) elderly euthymic patients with bipolar disorder who were on chronic lithium treatment and in 16 of 48 (33%) similar patients without recent lithium treatment [8], suggesting lithium effects on dementia. Although another study showed that patients who received lithium had a higher risk of dementia compared with those who did not [9], most of these findings suggest both possibilities that lithium may directly prevent dementia via its inhibition of GSK-3 and that lithium may indirectly prevent dementia via its prophylactic effects on mood episodes [10].

As shown in Table 1, 3 placebo-controlled studies have been performed to investigate lithium effects on dementia or mild cognitive impairment. Two studies showed lithium effects on dementia [11] and

mild cognitive impairment [12] whereas another study failed to show such effects [13]. It seems likely that lithium dose is not important because the successful 2 studies used completely different doses; routine doses (150-600 mg/day titrated to target serum levels of 0.25-0.5 mmol/l) [12] and microdose (300  $\mu$ g/day, serum levels were not measured) [11], respectively. Rather, administration period may be important because successful 2 studies administered lithium for 15 months [11] and 12 months [12], respectively whereas unsuccessful study gave lithium for only 10 weeks [13]. Therefore, further studies may be required to administer lithium for 12 months or longer to detect lithium effects on dementia or mild cognitive impairment. If administrative period is 12 months or longer, lithium doses can be much lower than usual because 300  $\mu$ g/day of lithium brought about the effects [11]. This possibility may evoke an interesting idea that lithium in drinking water can prevent dementia.

In addition to lithium effects on dementia, meta-analyses [14-16] have shown anti-suicidal effects of lithium in people with mood disorders, namely major depression and bipolar disorder, but these reviews have examined only randomized controlled trials that primarily compare lithium with placebo or other drugs in long-term prophylactic treatment of mood episodes (i.e., not anti-suicidal effects) which were maintained at so-called therapeutic levels. To date, there is only one study [17] that has directly compared anti-suicidal effects (but not prophylactic effects). In this 2.5-year double-blind randomized controlled trial, patients with bipolar disorder and past suicide attempts were randomly assigned to treatment with lithium or valproate conditions but no significant difference between the two treatments was found either in time to suicide attempt or number of suicide events, failing to show anti-suicidal effects of lithium.

Interestingly, there is growing evidence from epidemiological studies that lithium in drinking water may protect against suicide. An inverse association between lithium levels in drinking water and suicide rates was first reported in the USA for 27 Texas counties [18]. In Japan, an inverse association was shown between lithium levels in drinking water and suicide rates for 18 municipalities of Oita prefecture [19] whereas another study found no association for 47 subdivisions in the East of England [20]. A nationwide Austrian study, however, found an inverse association between lithium levels in drinking water and suicide rates after adjustment of population

**Table 1:** Placebo-controlled trials investigating lithium effects on dementia or mild cognitive impairment.

Authors	Subjects and methods	Results
Nunes et al (2013) [11]	113 patients with Alzheimer's disease were randomised to receive lithium (300 $\mu$ g/day) (n=58) or placebo (n=55) in a 15-month, double-blind trial.	Lithium group showed no decreased performance in the mini-mental state examination test, in opposition to the lower scores observed for placebo group, with significant differences starting 3 months after the beginning of the treatment, and increasing progressively.
Forlenza et al (2011) [12]	45 participants with a mild cognitive impairment were randomised to receive lithium (0.25-0.5 mmol/l) (n=24) or placebo (n=21) in a 12-month, double-blind trial.	Lithium treatment was associated with a significant decrease in phosphorylated tau of cerebrospinal fluid and better performance on the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-Cog) and in attention tasks.
Hampel et al (2009) [13]	71 patients with mild Alzheimer's disease were randomised to lithium treatment (0.5-0.8 mmol/l) (n=33) or placebo (n=38) in a 10-week, single-blind trial.	No treatment effect on glycogen synthase kinase-3 activity or phosphorylated tau of cerebrospinal fluid was observed. Lithium treatment did not lead to change in global cognitive performance as measured by the ADAS-Cog subscale or in depressive symptoms.

density, per capita income, proportion of Roman Catholics, as well as the availability of mental health service providers [21]. Recently, the Austrian group reconfirmed an inverse association between lithium levels in drinking water and suicide rates after adjustment of county-based population density, age, gender, race/ethnicity, median income per household, poverty and unemployment rates in Texas [22]. Very recently, 2 studies which were performed in Hirosaki prefecture of Japan [23] and in 34 prefectures of Greece [24] also reconfirmed the inverse association between lithium levels in drinking water and suicide rates.

Taking the above evidences together, further epidemiological studies are warranted to investigate the potential effects of environmental lithium in drinking water on dementia and suicide, both of which are very serious problems in the world.

## References

- Kessing LV, Olsen EW, Mortensen PB, Andersen PK. Dementia in affective disorder: a case-register study. *Acta Psychiatr Scand*. 1999; 100: 176-185.
- Kessing LV, Nilsson FM. Increased risk of developing dementia in patients with major affective disorders compared to patients with other medical illnesses. *J Affect Disord*. 2003; 73: 261-269.
- Kessing LV, Andersen PK. Does the risk of developing dementia increase with the number of episodes in patients with depressive disorder and in patients with bipolar disorder? *J Neurol Neurosurg Psychiatry*. 2004; 75: 1662-1666.
- Forlenza OV, de Paula VJ, Machado-Vieira R, Diniz BS, Gattaz WF. Does lithium prevent Alzheimer's disease? *Drugs Aging*. 2012; 29: 335-342.
- Kessing LV, Søndergård L, Forman JL, Andersen PK. Lithium treatment and risk of dementia. *Arch Gen Psychiatry*. 2008; 65: 1331-1335.
- Kessing LV, Forman JL, Andersen PK. Does lithium protect against dementia? *Bipolar Disord*. 2010; 12: 87-94.
- Terao T, Nakano H, Inoue Y, Okamoto T, Nakamura J, Iwata N. Lithium and dementia: a preliminary study. *Prog Neuropsychopharmacol Biol Psychiatry*. 2006; 30: 1125-1128.
- Nunes PV, Forlenza OV, Gattaz WF. Lithium and risk for Alzheimer's disease in elderly patients with bipolar disorder. *Br J Psychiatry*. 2007; 190: 359-360.
- Dunn N, Holmes C, Mullee M. Does lithium therapy protect against the onset of dementia? *Alzheimer Dis Assoc Disord*. 2005; 19: 20-22.
- Terao T. Lithium for prevention of Alzheimer's disease. *Br J Psychiatry*. 2007; 191: 361.
- Nunes MA, Viel TA, Buck HS. Microdose lithium treatment stabilized cognitive impairment in patients with Alzheimer's disease. *Curr Alzheimer Res*. 2013; 10: 104-107.
- Forlenza OV, Diniz BS, Radanovic M, Santos FS, Talib LL, Gattaz WF. Disease-modifying properties of long-term lithium treatment for amnesic mild cognitive impairment: randomised controlled trial. *Br J Psychiatry*. 2011; 198: 351-356.
- Hampel H, Ewers M, Bürger K, Annas P, Mörtberg A, Bogstedt A, Frölich L. Lithium trial in Alzheimer's disease: a randomized, single-blind, placebo-controlled, multicenter 10-week study. *J Clin Psychiatry*. 2009; 70: 922-931.
- Cipriani A, Pretty H, Hawton K, Geddes JR. Lithium in the prevention of suicidal behavior and all-cause mortality in patients with mood disorders: a systematic review of randomized trials. *Am J Psychiatry*. 2005; 162: 1805-1819.
- Baldessarini RJ, Tondo L, Davis P, Pompili M, Goodwin FK, Hennen J. Decreased risk of suicides and attempts during long-term lithium treatment: a meta-analytic review. *Bipolar Disord*. 2006; 8: 625-639.
- Cipriani A, Hawton K, Stockton S, Geddes JR. Lithium in the prevention of suicide in mood disorders: updated systematic review and meta-analysis. *BMJ*. 2013; 346: f3646.
- Oquendo MA, Galfalvy HC, Currier D, Grunebaum MF, Sher L, Sullivan GM. Treatment of suicide attempters with bipolar disorder: a randomized clinical trial comparing lithium and valproate in the prevention of suicidal behavior. *Am J Psychiatry*. 2011; 168: 1050-1056.
- Schrauzer GN, Shrestha KP. Lithium in drinking water and the incidences of crimes, suicides, and arrests related to drug addictions. *Biol Trace Elem Res*. 1990; 25: 105-113.
- Ohgami H, Terao T, Shiotsuki I, Ishii N, Iwata N. Lithium levels in drinking water and risk of suicide. *Br J Psychiatry*. 2009; 194: 464-465.
- Kabacs N, Memon A, Obinwa T, Stochl J, Perez J. Lithium in drinking water and suicide rates across the East of England. *Br J Psychiatry*. 2011; 198: 406-407.
- Kapusta ND, Mossaheb N, Etzersdorfer E, Hlavin G, Thau K, Willeit M. Lithium in drinking water and suicide mortality. *Br J Psychiatry*. 2011; 198: 346-350.
- Blüml V, Regier MD, Hlavin G, Rockett IR, König F, Vyssoki B. Lithium in the public water supply and suicide mortality in Texas. *J Psychiatr Res*. 2013; 47: 407-411.
- Sugawara N, Yasui-Furukori N, Ishii N, Iwata N, Terao T. Lithium in tap water and suicide mortality in Japan. *Int J Environ Res Public Health*. 2013; 10: 6044-6048.
- Giotakos O, Nisianakis P, Tsouvelas G, Giakalou VV. Lithium in the public water supply and suicide mortality in Greece. *Biol Trace Elem Res*. 2013; 156: 376-379.